

**REMARKS**

Claim 3 was objected to for being in improper dependent form. Claim 3 has been canceled and replaced by new claim 72, which depends from claim 62.

Claim 19 has also been canceled.

Prior to this Amendment, claims 1-23, 27-36, and 46-71 were pending. If this Amendment is entered, claims 1, 2, 4-18, 20-23, 27-36, and 46-72 will be pending. Claims 1, 2, 4-18, 20-23, 27-36, and 46-71 stand rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Perez et al., Nat. Med. 3:1228-1232 (1997) ("Perez") in view of U.S. Patent No. 5,712,262 to Spiegel ("Spiegel") and further in view of U.S. Patent No. 5,877,167 to Igarashi et al. ("Igarashi").

For reasons explained below, the Applicants respectfully traverse this rejection and ask that it be withdrawn.

**I. THE CLAIMED INVENTION**

All of the present claims are directed to treatments that are administered either *in vivo* (*i.e.*, on or inside the body of a mammal) or *ex vivo* (*i.e.*, a composition is initially administered outside the body of the mammal, *e.g.*, to tissue or cells, but the treated tissue or cells are then returned to the body of the mammal). The present claims thus stand in sharp contrast to treatments that occur *in vitro*, *i.e.*, completely outside the body of the mammal, in isolated tissues or cells.

For claims 27-36 and 46-61, the treatment is *in vivo*. Claims 27-32 recite that the composition is administered "to said mammal," and not, *e.g.*, to ovaries isolated from said mammal or to oocytes isolated from said mammal. Claims 33-36 recite that the composition is administered "to women." Claims 46-61 recite that the composition is administered "to a mammalian female patient."

For claims 1, 2, 4-18, 20-23, and 62-72, the treatment is either *in vivo* or *ex vivo*.

The present claims are directed to protecting the female reproductive system in various ways from artificial insults or natural insults where the insults occur *in vivo*.

**II. THE CITED REFERENCES**

Perez discloses studies in which sphingosine-1-phosphate was administered *in vitro* to isolated oocytes that were also treated *in vitro* with doxorubicin. See page 1228, left column, second line from bottom, where Perez states that the oocytes that were studied were “harvested [*i.e.*, isolated] from superovulated adult female mice” and “maintained in human tubal fluid medium under standard *in vitro* conditions.” See page 1229, Figure 2, and the discussion of Figure 2 in the left column, where Perez states that sphingosine-1-phosphate was administered to the isolated oocytes. Perez did not disclose studies in which sphingosine-1-phosphate was administered either *in vivo* or *ex vivo*. In Perez, the treated oocytes were never returned to the body, but were merely observed *in vitro*. Moreover, the insult (doxorubicin exposure) to the oocytes that were treated with sphingosine-1-phosphate occurred *in vitro*.

Spiegel is directed to “methods of retarding apoptosis in degenerative diseases, including neurodegenerative diseases and aging, …” (May 24, 2002 Office Action, page 3, 2<sup>nd</sup> paragraph). Spiegel disclosed the use of sphingosine-1-phosphate.

Igarashi is directed to “a method of inhibiting tumor cell chemoinvasion.” (May 24, 2002 Office Action, page 3, 3<sup>rd</sup> paragraph). Igarashi disclosed the use of sphingosine-1-phosphate.

Spiegel and Igarashi do not discuss oocytes or female reproduction.

### **III. DIFFERENCES BETWEEN THE CLAIMS AND THE CITED REFERENCES**

The present claims are directed to the *in vivo* or *ex vivo* use of compositions (including sphingosine-1-phosphate) to treat the female reproductive system to protect against an *in vivo* insult.

Perez is directed only to the *in vitro* use of sphingosine-1-phosphate and not its *in vivo* or *ex vivo* use. The use of sphingosine-1-phosphate in Perez is limited to use in conjunction with *in vitro* insults. Spiegel and Igarashi are not directed to treating the female reproductive system in any manner.

### **IV. THE REJECTION FOR OBVIOUSNESS**

The Examiner concluded that one of ordinary skill in the art would have combined Perez with Spiegel and Igarashi to arrive at the claimed invention. The reasons for this conclusion are given in the May 24, 2002 Office Action at page 5, line 4 to page 6, line 2:

Perez et al teaches that exposure of women to a wide spectrum of agents that damage the ovary generally leads to irreversible sterility (See e.g., p. 1228) and the data from the study provide a strong impetus to manipulate death effector pathways in oocytes, *in vivo*, as a potential means to overcome infertility associated with cancer treatment (See e.g., p. 1231). Spiegel teaches the use of sphingosine-1-phosphate (SPP) to retard apoptosis in degenerative diseases, including aging, which is defined by Applicant as a natural insult (See Applicant's specification, p. 15). Additionally, Spiegel teaches that SPP may be administered to the epithelial tissues, such as the rectum and the vagina (See e.g., Col. 1, line 46 to col. 2, line 26). Igarashi et al. provides methods of inhibiting tumor cell chemoinvasion, comprising administering to a host in need of treatment an inhibitory amount of sphingosine-1-phosphate and teaches that said inhibitory amount can be determined using art-recognized methods, such as dose response curves, or clinical trials, and sphingosine-1-phosphate can be administered orally, parenterally and topically (See e.g., col. 7, lines 32-65). Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to combine the teachings of Perez et al. and Spiegel to devise [sic, devise?] methods of protecting the female reproductive system, reviving the ovarian function or ameliorating menopausal syndromes in women, comprising administering SPP compositions, and determining the mode and dosage of administration according to the teachings of Igarashi et al. The expected result would have been a successful method of protecting a female reproductive system against natural or artificial insults.

## V. WHY THE REJECTION SHOULD BE WITHDRAWN

### A. THE CITED REFERENCES DO NOT PROVIDE A REASONABLE EXPECTATION OF SUCCESS FOR THE CLAIMED INVENTION

The Applicants contend that Perez, Spiegel, and Igarashi, in any combination, do not provide a reasonable expectation of success for the claimed invention.

It is well settled that a finding of obvious requires that the cited references provide a reasonable expectation of success for the claimed invention. It is not sufficient that the references make it obvious to try to make the claimed invention. See, e.g.,

In re Vaeck, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991), where the Federal Circuit said:

[A] proper analysis under §103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. See *In re Dow Chemical Co.*, 837 F2d 469, 473, 5 U.S.P.Q. 2d 1529, 1531 (Fed. Cir. 1988). [emphasis added]

Perez alone cannot provide a reasonable expectation of success for the claimed invention because:

- Perez is directed to an *in vitro* treatment (administering sphingosine-1-phosphate to isolated oocytes) to protect against an *in vitro* insult (administering doxorubicin to isolated oocytes).
- the present claims do not encompass *in vitro* treatments to protect against *in vitro* insults.
- Perez contains explicit statements of doubt as to whether Perez's *in vitro* results with isolated oocytes can be extrapolated to *in vivo* treatment of the female reproductive system as in the present claims. For example, Perez made it clear that *in vitro* effects are not predictive of *in vivo* successes such as preserving ovarian function. See page 1231, sentence bridging left and right columns:

Despite the significant advances made by this study in defining the biochemical and genetic pathways involved in oocyte destruction following exposure to anticancer drugs, future long-term studies are required to confirm that inhibiting germ cell apoptosis will preserve ovarian function. [emphasis added]

Perez also taught that *in vivo* treatments of the female reproductive system (*e.g.*, preserving its fertility) require an effect not just on oocytes, but also on the follicles that support oocytes. See page 1230, lines 6-7: “[F]ertility preservation would require maintenance of the entire follicle and not solely the oocyte.” Perez, page 1230, col. 1, lines 6-7. Perez contains no demonstration of the effects of sphingosine-1-phosphate on follicles and thus cannot provide a reasonable expectation of success for treatments that depend on effects on follicles.

With respect to what implications Perez's *in vitro* results have for *in vivo*

methods such as those presently claimed, the Examiner stated: “[T]he data from the study [*i.e.*, from Perez] provide a strong impetus to manipulate death effector pathways in oocytes, in vivo, as a potential means to overcome infertility associated with cancer treatment.” [first underlining added] (May 24, 2002 Office Action, page 3, lines 5-7 and page 5, lines 6-8)

The Applicants believe that the statement quoted above demonstrates at most that Perez makes it obvious to try the claimed invention. This is supported by the Examiner’s use of the word “impetus” which speaks to motivation or suggestion rather than expectation of success.

The Examiner did not argue that Perez alone provided a reasonable expectation of success. The Examiner instead argued that it was the combination of Spiegel and Igarashi with Perez that provided a reasonable expectation of success. There is only one statement in the Office Action dated May 24, 2002 that contains a reasoned argument as to why the Spiegel and Igarashi references might provide a reasonable expectation of success for the claimed invention. See page 4, 2<sup>nd</sup> paragraph, lines 5-9:

Because of the teachings of Spiegel, that sphingosine-1-phosphate is effective in treating aging diseases, and the teachings of Igarashi et al., that sphingosine-1-phosphate inhibits tumor cell chemoinvasion, one of ordinary skill in the art would have a reasonable expectation that the methods claimed in the instant application would be successful.

In other words, the Examiner is relying on references directed to neurodegenerative aging diseases and the metastasis of tumor cells in order to provide a reasonable expectation of success for an invention directed to the in vivo protection of the female reproductive tract! These three types of health problems have no obvious connection and the Examiner has not provided an explanation of why they might be connected. The Applicants do not understand how the expressions of doubt as to reasonable expectation of success in Perez quoted above can be negated by two references that are directed to entirely different health problems from those of both Perez and the present claims.

## B. THE CITED REFERENCES SHOULD NOT BE COMBINED

That the Examiner could not explain how the cited references might provide a reasonable expectation of success is not surprising when one considers the content of the

references. Spiegel and Igarashi cannot bridge the gap between Perez's *in vitro* results in oocytes and the Applicants' *in vivo* invention directed to female reproduction because Spiegel and Igarashi have absolutely nothing to do with oocytes or female reproduction.

Spiegel is directed to "methods of retarding apoptosis in degenerative diseases, including neurodegenerative diseases and aging, ..." (May 24, 2002 Office Action, page 3, 2<sup>nd</sup> paragraph). Igarashi is directed to "a method of inhibiting tumor cell chemoinvasion."<sup>1</sup> (May 24, 2002 Office Action, page 3, 3<sup>rd</sup> paragraph). The Examiner never contends that Spiegel or Igarashi discuss oocytes or female reproduction.

Spiegel and Igarashi are not directed to the field of the Applicants' invention, mammalian female reproduction. Nor are Spiegel and Igarashi directed to the particular problems solved by the present claims: protecting a female reproductive system against an artificial insult (claims 1, 2, 4-18, and 20-23); preserving, enhancing, or reviving ovarian function (claims 27-32); preventing or ameliorating menopausal syndromes (claims 32-36); protecting a female reproductive system from damage caused by treatment for a disease, disorder, or condition (claims 46-61); and protecting a female reproductive system against an natural insult (claims 62-72).

References that are directed neither to the field of the applicant's invention or to the particular problem with which the applicant is concerned may not be used to support an obviousness rejection. See, e.g., In re Oetiker, 977 F.2d 1443, 1447, 24 USPQ2d 1443:

In order to rely on a reference as a basis for rejection of the applicant's invention, the reference must either be in the field of the applicant's endeavor, or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned.

Since Spiegel and Igarashi are directed neither to the field of the Applicants' invention or to the particular problem with which the Applicants were concerned, Spiegel and Igaraashi should not have been combined with Perez.

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The time for responding to the Office Action was set for August 24, 2002. Enclosed herewith is a Petition for the Extension of Time under 37 C.F.R. § 1.136(a) for a period sufficient to permit the filing of this response.

The Applicants hereby also make a Conditional Petition for any relief available to correct any defect seen in connection with this filing, or any defect seen to be remaining in this application after this filing. The Commissioner is authorized to charge Kenyon & Kenyon's Deposit Account No. 11-0600 for any fees associated with such Conditional Petition.

**CONCLUSION**

For at least the reasons discussed above, the present claims are not obvious over Perez, Spiegel, and Igarashi, taken alone or in any combination.

Applicants submit that the subject application is in condition for allowance, and respectfully request that such action be taken. The Examiner is invited to contact the undersigned to discuss any matter regarding this application.

Respectfully submitted,  
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